Endogenously oscillating motoneurons produce undulatory output in a connectome-based neuromechanical model of C. elegans without proprioception

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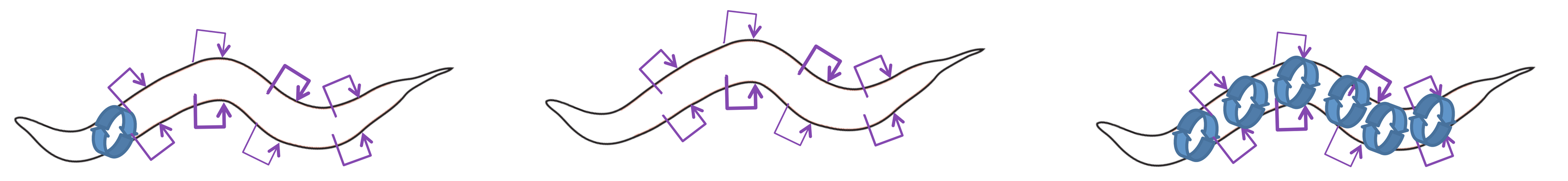
Introduction

Nematodes generate thrust by propagating dorsoventral body bends along their body against the direction of locomotion. In *Caenorhabditis elegans*, all the neurons and muscle that compose the locomotion system are known, as well as their connectivity, yet the neural mechanisms responsible for the production of coordinated muscle activity remain poorly understood. In this modeling study, we investigate whether a chain of oscillators distributed along the body of *C. elegans* can generate a meaningful motor pattern, without sensory feedback?

Hypotheses

Head oscillator, sensory propagation | All sensory feedback | A chain of oscillators



Niebur and Erdos (1993)
Karbowski et al (2008)
Wen et al (2012)

Boyle et al (2012)
Cohen and Sanders (2014)

Gjorgjieva et al (2014)

Iterating connectivity deduced from EM data

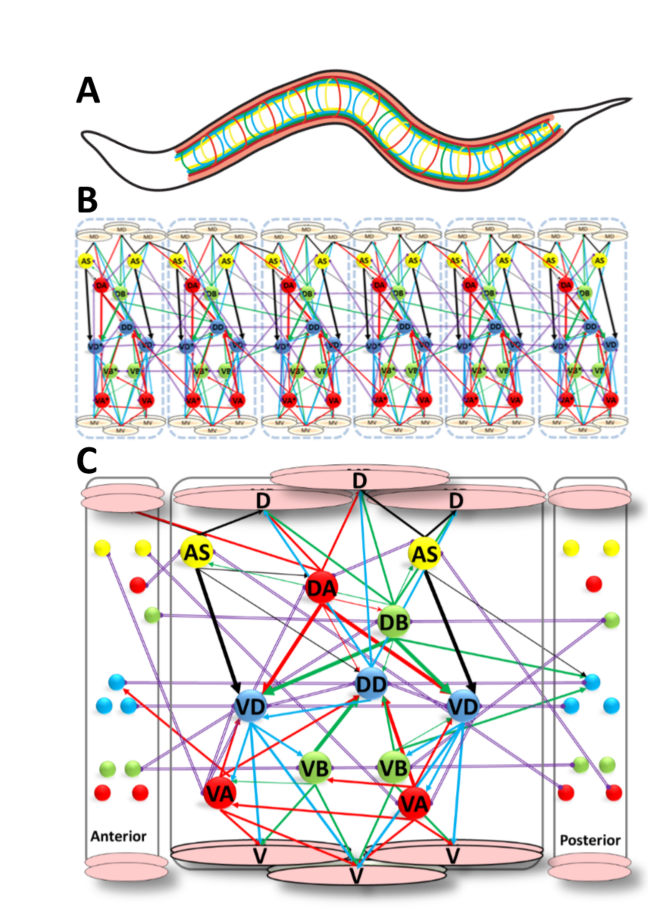


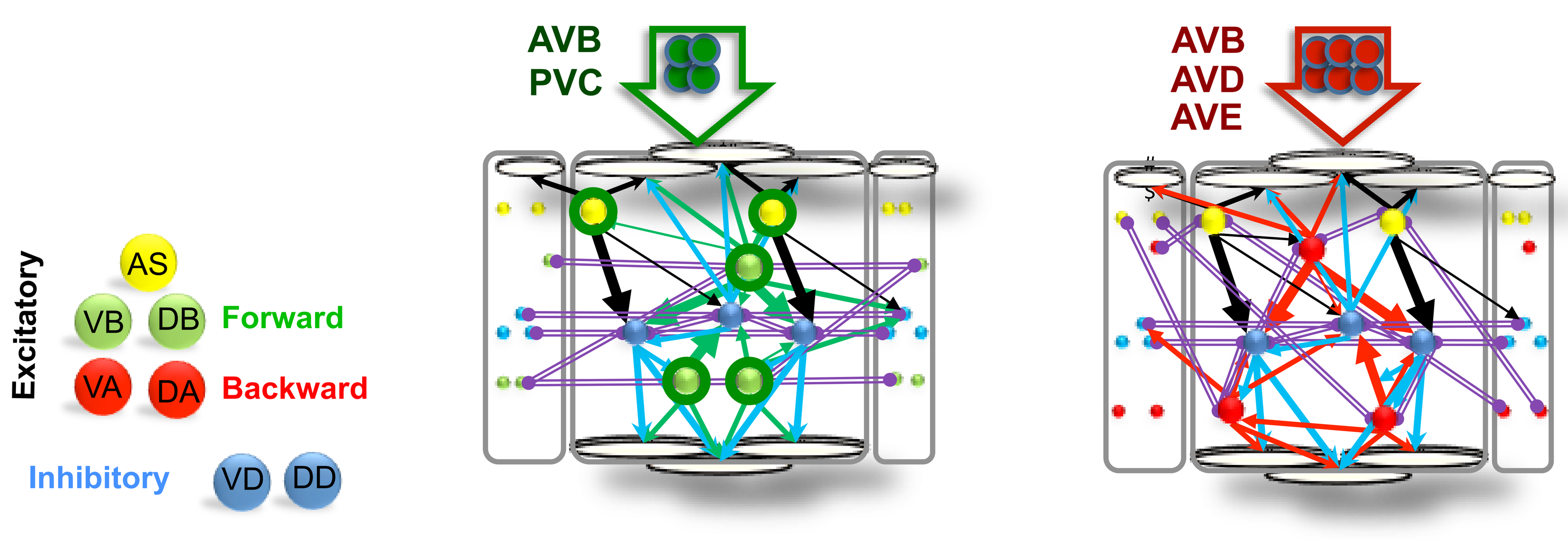
Fig. 1: Distribution of oscillators tested in data-based connectivity .

The only existing organism-wide connectivity dataset (connectome) is that of C. elegans. It was reconstructed by White and colleagues in 1986 from electromicrographs. Of the animal's 302 neurons, about 30 have missing or partial data, all in the posterior portion of the locomotion network.

We previously reported (Haspel and O'Donovan 2011) that iterative connectvity in the anterior portion can be extrapolated to complete the network. The neurons and muscle compose functional repeating units, each (as shown in Fig 1 C) with 11 neurons and 6 muscle pairs. Six repeating units are interconnected to complete a connectivity model of the locomotion network, including neurons, muscle cells and all connections.

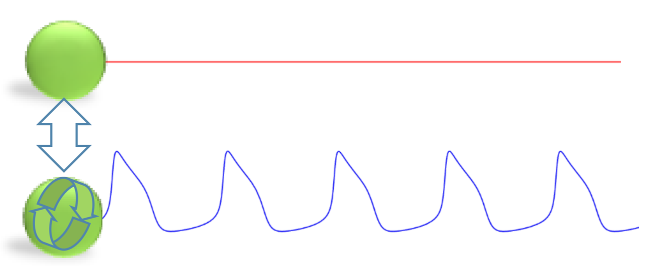
Forward and backward locomotion are induced by two groups of interneurons

Five pairs of interneurons are the main descending input to the locomotion network and seem to select the direction of movement. The "forward interneurons" (;eft and right AVB and PVC) innervate the AS, DB and VB motoneurons, while the "backward interneurons" (left and right AVA, AVD and AVE) innervate AS, DA and VA. The inhibitory D-motoneurons are only innervated by other motoneurons.



Cells were modeled either as "oscillator" or "passive"

We use single set of equations (based on *Huber-Braun* model) to populate the network with neurons that are either "passive" or "oscillators". IAVA and IAVB are parameters representing input currents from interneurons external to the network that are related to backward and forward motion. Cells within the networj are connected via gap junctions, excitatory synapses and inhibitory synapses.



$$C\frac{dV}{dt} = I_{AVA} + I_{AVB} - I_{SD} - I_{SR} - I_L - I_{gap} - I_{syne} - I_{syni}$$

$$I_{gap} = g_{gap}\left(V_i - \sum_{i=1}^{n} V_i\right)$$

$$I_{syne} = g_{syne}\sum_{i=1}^{n} s_i (V_j - E_{syne})$$

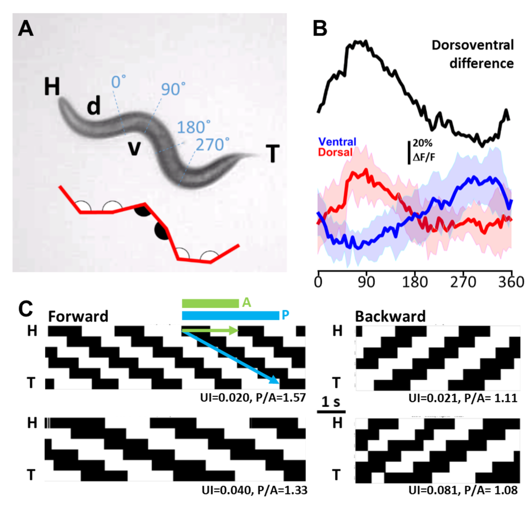
$$I_{syni} = g_{syni}\sum_{i=1}^{n} s_i (V_j - E_{syni})$$

$$\frac{ds}{dt} = \alpha(V_j)(1-s) - \beta s$$

$$\frac{da_{sd}}{dt} = \frac{a_{sd\infty}(V) - a_{sd}}{\tau_{sd}}$$

$$\frac{da_{sr}}{dt} = \frac{-\rho I_{SD} - a_{sr}}{\tau_{sr}}$$

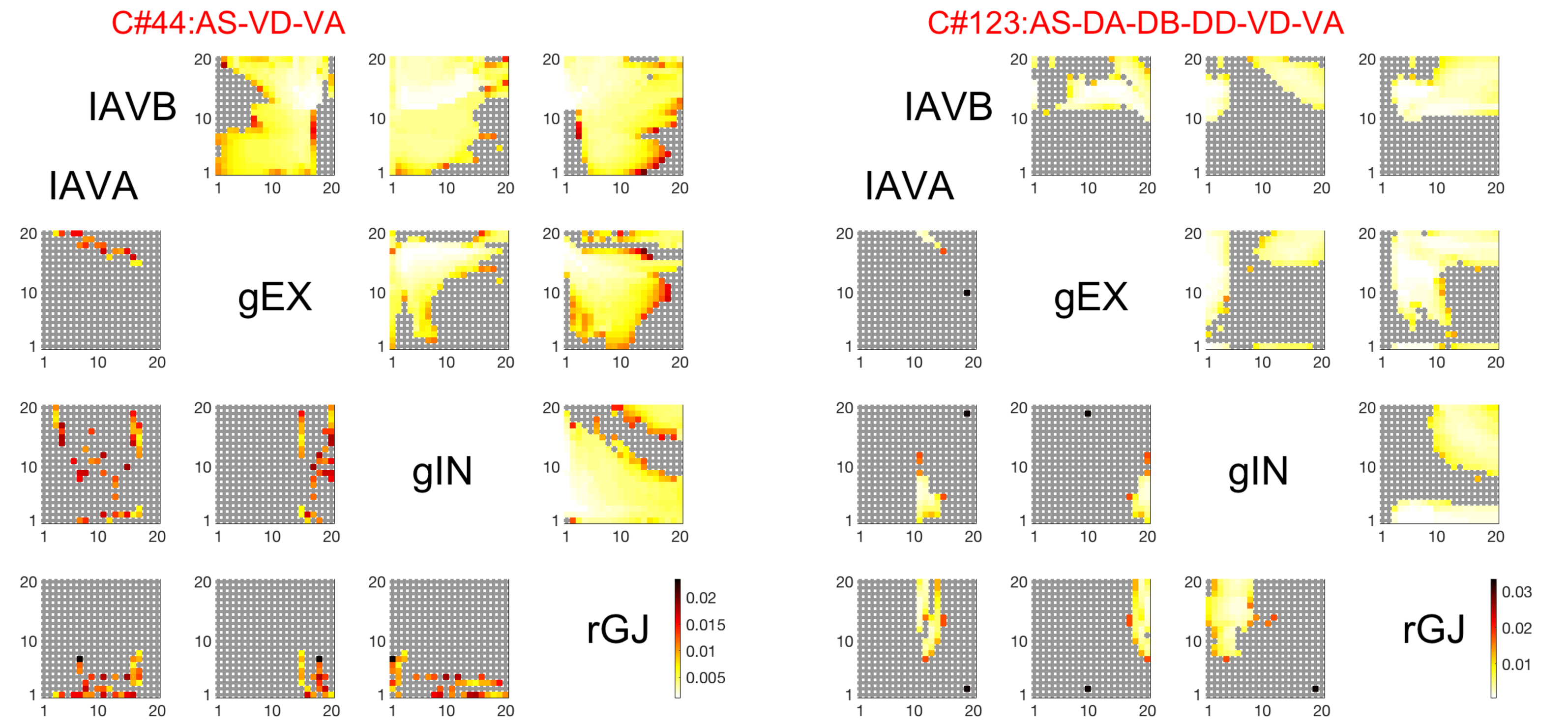
Animals undulate by overlapping segment bends, prpagation slower than alternation, and low phase variability



We used real locomotion behavior to define model output as undulation. Criteria for undulations were propagation, phase overlaps and P>A. Undulation index (UI) is defined as variability of phase.

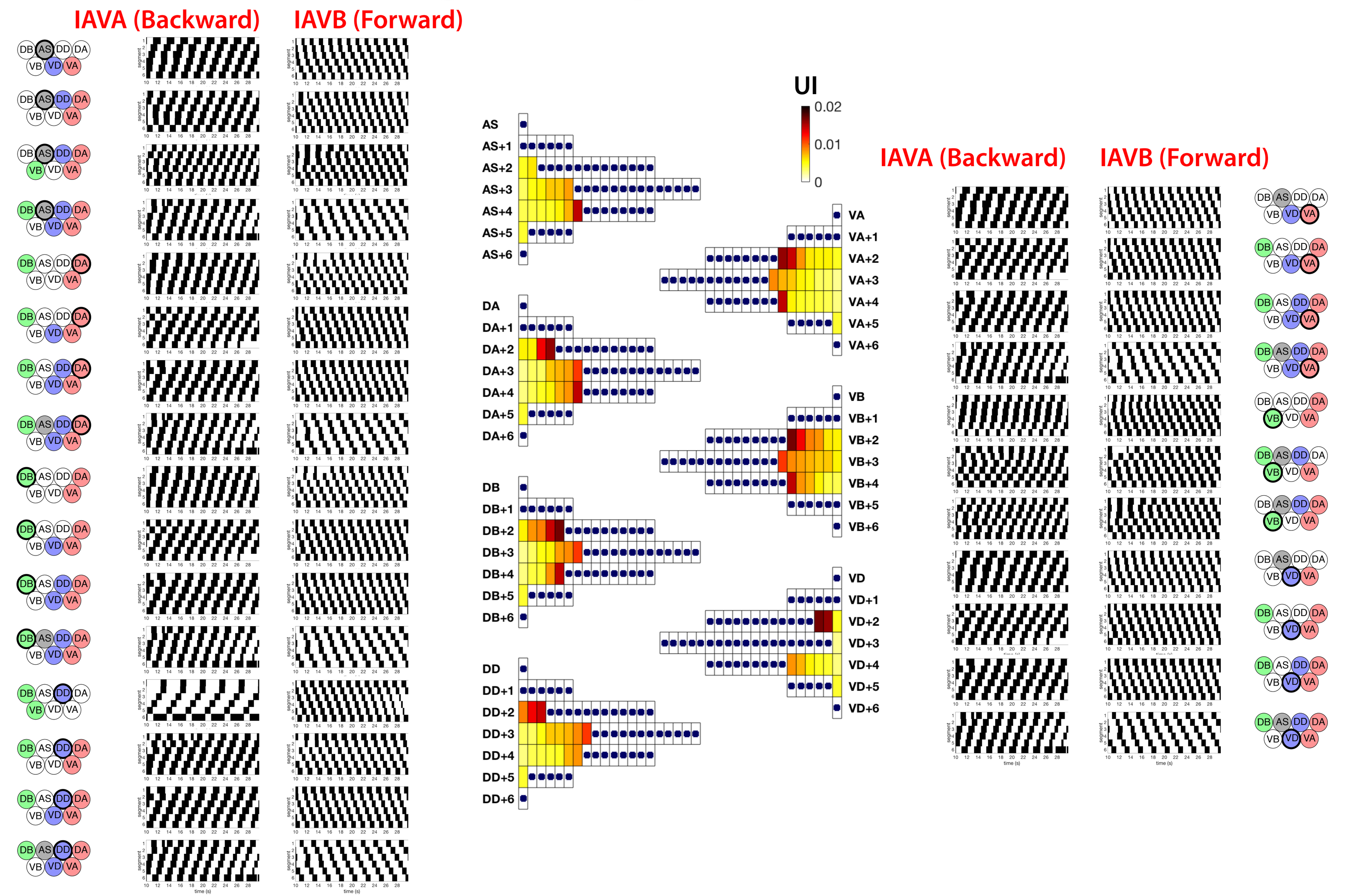
While using UI for the comparison of models, we also used number of complete cycles during the last 20 sec of simulations.

Parameter sweeps mapped which parameter sets generate meaningful output

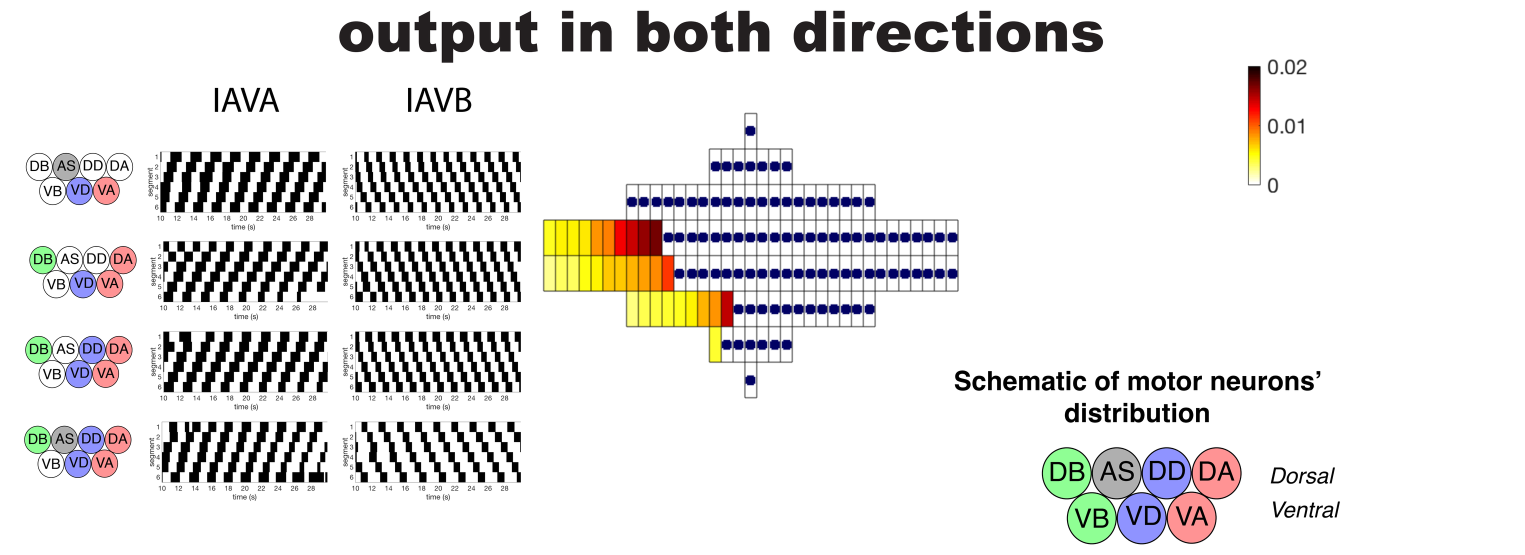


128 combinations * 2 directions * 20 values each parameter ^ 4 free parameters = 40,960,000 parameter sets analyzed

VA, DA and DB motoneurons are involved in most meaningful output combinations



Three to six classes of motoneurons give robust output in both directions



Conclusions:

1. Using the known architecture and connectivity, the locomotion circuit produces an undulatory pattern, without proprioception, when some motoneuron classes are oscillators.
2. It is easier to produce a meaningful output when about half of the motoneuron classes are oscillators.
3. Motoneuron identity is important. Excitatory motoneurons (specifically in C. elegans, AS and VA) are the most effective in generating a meaningful output.